

Polish Forum for Prevention Guidelines on Metabolic Syndrome

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Introduction

Metabolic syndrome (MS) means the coexistence of several risk factors for cardiovascular diseases (CVD) and diabetes with a frequency higher than could result from chance. Its definition, significance and even existence have been the subject of many controversies. Eleven years have passed since the first official definition of MS introduced in 1999 by the World Health Organization (WHO) [1], which is summarized in Table I. Its use in clinical practice is rare because tests such as albuminuria or metabolic clamp technique to assess insulin resistance are not readily accessible and thus are rarely used in general practice. A more clinician-friendly definition was proposed by the National Cholesterol Education Program – Adult Treatment Panel III (NCEP-ATP III) in 2001 (Table II) [1], which does not require special testing for glucose beyond routine clinical assessment. Furthermore, it does not require any specific criterion to be met. In the modified version of this definition in 2005 the threshold for impaired fasting glucose (IFG) was reduced from 110 to 100 mg/dl [2], which

corresponded to the modified American Diabetes Association (ADA) [3] criteria for IFG. In the same year, the International Diabetes Foundation (IDF) published new criteria (Table III) [3] that again modified the ATP III definition. They considered insulin resistance as an essential part of MS and made abdominal obesity, which is highly correlated with this abnormality, necessary for diagnosis of MS. When this is present, 2 additional factors originally listed in the ATP III definition are sufficient for diagnosis. IDF additionally recognized and emphasized ethnic differences in the correlation between abdominal obesity and other MS components and the risk of CVD risk and diabetes. Thus different thresholds for abdominal obesity were proposed for specific populations, for example for people of European origin ≥ 94 cm in men and ≥ 80 cm in women, for South Asian populations ≥ 90 cm in men and ≥ 80 cm in women, and for Japanese ≥ 85 cm for men and ≥ 90 cm for women.

Recently 6 major organizations – the IDF Task Force on Epidemiology and Prevention; the National Heart, Lung, and Blood Institute; the American Heart Association; the

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Table I. World Health Organization (WHO) Clinical Criteria for Metabolic Syndrome**Insulin resistance, identified by 1 of the following:**

- type 2 diabetes
- impaired fasting glucose
- impaired glucose tolerance
- glucose uptake below the lowest quartile for background population under investigation under hyperinsulinaemic, euglycaemic conditions

Plus any 2 of the following:

- antihypertensive medication and/or high blood pressure (≥ 140 mmHg systolic or ≥ 90 mmHg diastolic)
- plasma triglycerides ≥ 150 mg/dl (1.7 mmol/l)
- HDL cholesterol < 35 mg/dl (0.9 mmol/l) in men or < 39 mg/dl (1.0 mmol/l) in women
- BMI ≥ 30 kg/m² and/or waist:hip ratio > 0.9 in men, > 0.85 in women
- urinary albumin excretion rate ≥ 20 μ g/min or albumin: creatinine ratio ≥ 30 mg/g

World Heart Federation; the International Atherosclerosis Society; and the International Association for the Study of Obesity – have joint together to propose unified criteria for MS [4]. They suggest that there should not be an obligatory component to diagnose MS (as suggested in the ATP III definition) but it is necessary to use different cut-off points for abdominal obesity regarding the characteristics of the population (as suggested in the IDF criteria); they underscored however that further evidence from prospective studies is needed in the second field.

Table II. National Cholesterol Education Program Adult Treatment Panel III (NCEP-ATP III) criteria for Metabolic Syndrome**Three of the following risk factors must be present to diagnose metabolic syndrome:**

- abdominal obesity, given as waist circumference ≥ 102 cm in men and ≥ 88 cm in women
- triglycerides ≥ 150 mg/dl
- HDL cholesterol
men < 40 mg/dl
women < 50 mg/dl
- blood pressure $\geq 130/\geq 85$ mmHg
- fasting glucose ≥ 110 mg/dl*

* In the 2005 modifications of these guidelines the threshold for impaired fasting glucose was lowered to 100 mg/dl (5.6 mmol/l).

This new definition has been incorporated in the presented Polish Forum for Prevention (PFP) [5] Guidelines on MS.

In the current consensus we refer to previous PFP guidelines [6-12] because the assessment and treatment of a specific component of MS is usually not significantly different than in patients without MS. However, the important message from these guidelines is that recognition of one risk factor of MS should encourage physicians to look for others. It should be underscored that the guidelines on management of hypertension in MS have been changed in comparison to the PFP Guidelines on Hypertension published in 2007, which is due to the latest Reappraisal of the European guidelines on hypertension management [13].

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Table III. International Diabetes Federation definition of Metabolic Syndrome**Central obesity defined as increased waist circumference with ethnicity specific thresholds.****Plus any two of the following factors:**

- raised TG level: ≥ 150 mg/dl (1.7 mmol/l), or specific treatment for this lipid abnormality
- reduced HDL cholesterol: < 40 mg/dl (1.0 mmol/l) in males and < 50 mg/dl (1.3 mmol/l) in females, or specific treatment for this lipid abnormality
- raised blood pressure: systolic BP ≥ 130 or diastolic BP ≥ 85 mmHg, or treatment of previously diagnosed hypertension
- raised fasting plasma glucose (FPG) ≥ 100 mg/dl (5.6 mmol/l), or previously diagnosed type 2 diabetes

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Guidelines

1. **Metabolic syndrome (MS)** is a clinical state characterized by clustering of several factors – central obesity, raised blood pressure, lipid and carbohydrate metabolism abnormalities – that increase the risk of development and progression of cardiovascular diseases (CVD) and diabetes.
2. **Pathomechanism of MS** – insulin resistance, obesity (especially abdominal), and proinflammatory state play the key roles. They result from interaction of demographics, lifestyle (low physical activity, unhealthy diet), genetic factors and environmental fetal programming.
3. **Diagnostic criteria for MS** used in clinical practice in people ≥ 16 years old:
 - a. waist circumference ≥ 94 cm in men and ≥ 80 cm in women,
 - b. elevated triglycerides ≥ 150 mg/dl (1.7 mmol/l) or specific treatment for this lipid abnormality (fibrates, nicotinic acid, high dose omega-3 fatty acids),
 - c. low HDL cholesterol < 40 mg/dl (< 1.0 mmol/l) in men and < 50 mg/dl (1.3 mmol/l) in women or specific treatment for this lipid abnormality (fibrates and nicotinic acid),
 - d. raised blood pressure: systolic ≥ 130 mmHg and/or diastolic ≥ 85 mmHg or treatment of previously diagnosed hypertension,
 - e. fasting plasma glucose ≥ 100 mg/dl (5.6 mmol/l) or treatment with hypoglycaemic drugs.
 To diagnose MS ≥ 3 criteria must be fulfilled.
 In children MS can be diagnosed ≥ 10 years of age when ≥ 3 of the following risk factors are present: central obesity (waist circumference ≥ 90 pc.), triglyceride level ≥ 150 mg/dl (1.7 mmol/l), HDL cholesterol ≤ 40 mg/dl (1.0 mmol/l), blood pressure $\geq 130/85$ mmHg and fasting glucose ≥ 100 mg/dl (5.6 mmol/l).
4. **The prevalence of MS** defined according to modified NCEP-ATP III (National Cholesterol Education Program, Adult Treatment Panel III) criteria in the general population of Polish adults aged 20-74 is 23% in men and 20% in women and reaches almost 50% in older groups. The most frequent abnormality is elevated blood pressure (69% of men with MS and 50% of women with MS), followed by elevated triglycerides in men (34% of men with MS) and abdominal obesity in women (41% of women with MS).
5. **MS increases the risk** of diabetes (3-6 times), CVD events and all-cause death (2 times).
 Cardiovascular diseases risk in persons with MS is increased (when compared to persons without MS) in the general population as well as in patients with diabetes and CVD. Coexistence of other risk factors, e.g. smoking, additionally increases the risk. MS predisposes to early organ damage such as left ventricle hypertrophy, microalbuminuria, arterial stiffness, thickening of intima-media complex in carotid arteries, and endothelial dysfunction, and promotes the prothrombotic state, which increases the risk of venous thrombosis and pulmonary thromboembolism.
6. **Diagnosis of MS** – recognition of one component of MS is an indication for active search for other components and assessment of total CVD risk with classic risk scales such as SCORE charts (see the Polish Forum for Prevention Guidelines on Cardiovascular Risk Assessment).
 In patients with MS and without diabetes the oral glucose tolerance test should be done. Total CVD risk in individuals with MS may be higher than estimated by the SCORE system so it is advised to actively search for early organ damage, whose prevalence in MS increases (see the Polish Forum for Prevention

Guidelines on Arterial Hypertension). Its identification may change the risk category in an individual.

7. **Treatment of MS** is aimed at decreasing the risk of diabetes, hypertension, organ damage and CVD risk and should be oriented at all components of MS. The first choice therapy is weight loss, which can be achieved by a decrease in intake of calories (500-1000 per day) and increase in physical activity (at least 30 min of moderate physical activity a day). The goal is a 7-10% reduction of initial weight in 6-12 months (see the Polish Forum for Prevention Guidelines on Overweight and Obesity). It is indicated to modify the diet (see the Polish Forum for Prevention Guidelines on Diet) and to stop smoking (see the Polish Forum for Prevention Guidelines on Smoking).
8. **Hypertension** in individuals with MS – in its development, the following mechanisms connected with obesity and insulin resistance should be considered: increased sympathetic activity, stimulation of the renin-angiotensin-aldosterone system, abnormal renal sodium uptake and endothelial dysfunction. Pharmacotherapy of hypertension is indicated when blood pressure is $\geq 140/90$ mmHg. It is indicated to reduce blood pressure to about 130/80 mmHg. The first choice drugs are angiotensin-converting enzyme inhibitors and angiotensin receptor blockers (sartans). The second choice drugs are: calcium channel

blockers and beta blockers with vasodilative effects (carvedilol and nebivolol). Diuretics should be used only in low doses and in combination with other hypotensive drugs. The use of other beta blockers and the combination of beta blockers with diuretics should be avoided unless there is a significant indication.

9. **Atherogenic dyslipidaemia** is a specific lipid abnormality found in MS which consists of: hypertriglyceridaemia, low HDL cholesterol concentration and presence of small dense LDL. The treatment of dyslipidaemia in patients with MS should follow the general rules (see the Polish Forum for Prevention Guidelines on Dyslipidaemia).
10. **Diabetes** in patients with MS – management of obese patients with MS is based on behavioural and pharmacological treatment. The preferred drug is metformin used in monotherapy and in combination with other drugs. In combination therapy acarbose can also be used. Among the less proven classes of drugs with potential beneficial effects in patients with MS are glitazones and incretins (glucagon-like peptide-1 agonists and dipeptidyl-peptidase IV inhibitors). Management with metformin should be considered in patients with MS and pre-diabetes when non-pharmacological intervention is not effective (see the Polish Forum for Prevention Guidelines on Diabetes).